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Research

Global estimate of the incidence of clinical pneumonia among children under five years of age

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Objective Clinical pneumonia (defined as respiratory infections associated with clinical signs of pneumonia, principally pneumonia and bronchiolitis) in children under five years of age is still the leading cause of childhood mortality in the world. In this paper we aim to estimate the worldwide incidence of clinical pneumonia in young children.

Methods Our estimate for the developing world is based on an analysis of published data on the incidence of clinical pneumonia from community-based longitudinal studies. Among more than 2000 studies published since 1961, we identified 46 studies that reported the incidence of clinical pneumonia, and 28 of these met pre-defined quality criteria.

Findings The estimate of the median incidence from those studies was 0.28 episodes per child-year (e/cy). The 25–75% interquartile range was 0.21–0.71. We assessed the plausibility of this estimate using estimates of global mortality from acute respiratory infections and reported case-fatality rates for all episodes of clinical pneumonia reported in community-based studies or the case-fatality rate reported only for severe cases and estimates of the proportion of severe cases occurring in a defined population or community.

Conclusion The overlap between the ranges of the estimates implies that a plausible incidence estimate of clinical pneumonia for developing countries is 0.29 e/cy. This equates to an annual incidence of 150.7 million new cases, 11–20 million (7–13%) of which are severe enough to require hospital admission. In the developed world no comparable data are available. However, large population-based studies report that the incidence of community-acquired pneumonia among children less than five years old is approximately 0.026 e/cy, suggesting that more than 95% of all episodes of clinical pneumonia in young children worldwide occur in developing countries.

Keywords Pneumonia/epidemiology/mortality; Bronchiolitis/epidemiology/mortality; Child, Preschool; Incidence; Longitudinal studies; Meta-analysis; Developing countries (*source: MeSH, NLM*).

Mots clés Pneumonie/épidémiologie/mortalité; Bronchiolite/épidémiologie/mortalité; Enfant âge pré-scolaire; Incidence; Etude longitudinale; Méta-analyse; Pays en développement (*source: MeSH, INSERM*).

Palabras clave Neumonía/epidemiología/mortalidad; Bronquiolitis/epidemiología/mortalidad; Preescolar; Incidencia; Estudios longitudinales; Meta-análisis; Países en desarrollo (*fuentes: DeCS, BIREME*).

الكلمات المفتاحية: الالتهاب الرئوي، وبائيات الالتهاب الرئوي، معدل الوفيات الناجمة عن الالتهاب الرئوي؛ التهاب القصبيات، وبائيات التهاب القصبيات، معدل الوفيات الناجمة عن التهاب القصبيات؛ الأطفال دون سن الالتحاق بالمدرسة؛ معدل الوقوع؛ دراسات طولانية؛ التحليل التلوي؛ البلدان النامية (المصدر: رؤوس الموضوعات الطبية المكتب الإقليمي لشرق المتوسط)

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Voir page 901 le résumé en français. En la página 901 figura un resumen en español.

يمكن الاطلاع على الملخص بالعربية في صفحة 902.

Introduction

Acute respiratory infections (ARI) in children less than five years old are the leading cause of childhood mortality in the world. Most of these deaths are caused by pneumonia and bronchiolitis. WHO estimated that the annual number of ARI-related deaths in this age group (excluding those caused by measles and pertussis and neonatal deaths) was 2.1 million (1), accounting for about 20% of all childhood deaths. This was

based largely on estimates of mortality published by Williams et al. (2). The primary aim of this paper is to estimate the incidence of pneumonia and bronchiolitis in the developing world. This can be considered a close approximation of the global incidence of these conditions because nearly 90% of children less than five years old live in developing countries (2), and the incidence of these diseases is substantially greater among children in developing countries (3, 4). This work was

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commissioned and directed by the Child Health Epidemiology Reference Group (CHERG) which is coordinated by the Department of Child and Adolescent Health (CAH) of WHO, and the estimates obtained were subject to critical review by this group.

Acute lower respiratory infections (ALRI) are defined in the *International statistical classification of diseases and related health problems, tenth revision*, as those infections that affect the airways below the epiglottis. These include acute manifestations of laryngitis, tracheitis, bronchitis, bronchiolitis, lung infections, any combination of these, or any of these along with upper respiratory infections, including influenza. The focus of the global burden of disease programme has been on conditions accounting for a substantial loss of disability-adjusted life years. Within CHERG, a decision was made to concentrate on pneumonia and bronchiolitis because these are considered to be the major components of ALRI that account for the global burden of disease from acute respiratory infections among young children. This approach is consistent with the WHO approach to the case management of ARI, which was introduced first by the programme for the control of ARI in order to standardize and facilitate clinical decision-making in places with limited resources and which has now been incorporated into the global Integrated Management of Childhood Illness, or IMCI, programmes. IMCI programmes train health workers to identify fast breathing, lower chest wall indrawing or selected danger signs in children with respiratory symptoms (such as cyanosis or an inability to drink). For the programme's purposes, these are labelled "pneumonia", although it is recognized that children identified in this way include those with pneumonia, bronchiolitis and a proportion of those with reactive airways disease associated with a respiratory infection. The studies reviewed in this paper have adopted this approach and we have called the conditions identified "clinical pneumonia". The review thus reports episodes of pneumonia, bronchiolitis and, in some studies, reactive airways disease associated with respiratory infections; it does not report episodes of acute laryngitis, bronchitis or tracheitis.

Methods

Our estimate is based on an analysis of published data on the incidence of clinical pneumonia from community-based longitudinal studies that met pre-defined quality criteria (5–32). We assessed the plausibility of our estimate (and the internal consistency of incidence, mortality and case-fatality data) in two ways. The first approach was based on the reported total number of childhood deaths due to ARI (1) and our best approximation of the case-fatality rate from all cases of clinical pneumonia in a community (21, 22, 33, 34). The second approach was based on the reported total number of childhood deaths due to ARI (1), reported case-fatality rates only for severe episodes of clinical pneumonia (those that require hospital admission) (26, 35–45), and estimates of the proportion of severe cases in a defined population or community (1, 5, 8, 20, 23, 46, 47).

Box 1 details the research plan. The initial literature review was performed by searching Medline, Science Citation Index and Current Contents for data from the period 1961–2000. Search terms included acute (lower) respiratory infections, bronchiolitis, croup, pneumonia, tracheobronchitis, children, under five years, developing countries, incidence, mortality, epidemiology, and combinations of these terms. Free text searches

were performed in the title and abstract fields in PubMed and Ovid. The WHO library database (WHOLIS) was searched for journals, documents, publications and reports not indexed on Medline. Additional electronic databases searched included the WHO Statistical Information System (WHOSIS), UNICEF, the UN Population Division, and the US Centers for Disease Control and Prevention's National Center for Health Statistics database; this last resource also pointed us towards significant reports from unpublished "grey" literature including national reports and unpublished studies (A Marx, unpublished data, 2000).

After reviewing more than 2000 studies, we selected the most informative studies. These studies estimated the incidence of clinical pneumonia among children less than five years old in a developing country or provided information that helped us to understand the determinants of clinical pneumonia occurrence, aetiology, clinical features, management, case-fatality rate or outcome in developing countries. A pre-defined set of key data was extracted systematically from each study and recorded in an electronic database. (This information is available from http://www.who.int/child-adolescent-health/New_Publications/Overview/ari_db.htm.)

The review then focused on studies that met the minimum quality criteria (Box 1). The minimum criteria were that:

- community-based surveillance of a defined population of children had to have been carried out for a minimum period of one year (and in multiples of 12 months) because clinical pneumonia has such a markedly seasonal nature;
- the study had to use a strategy of active case detection. The surveillance interval had to be 2 weeks or shorter to minimize recall bias;
- case definitions had to be clearly defined and consistently applied.

Applying these criteria yielded 28 studies that formed the basis of this review. Their geographical distribution and reported incidence rates are shown in Fig. 1, and their characteristics are summarized in Table 1, web version only, available at: <http://www.who.int/bulletin>.

An attempt was made to ensure that the reported incidence rates across a full age range of 0–4 years were comparable between the studies. When different incidence rates were provided for several cohorts within the same study (e.g., separately by village or sex), a weighted mean was calculated. In cases where intervention studies were undertaken, only the incidence rate in the control ("no intervention") arm of the trial was used in the analysis. When studies reported incidence only for restricted age ranges of children (e.g., 0.5–3 years), an adjustment to the full age range was performed. This was based on the mean age-specific incidence ratios obtained from five studies that reported incidence separately for each of the 1-year age groups (5, 14, 26, 27, 32). Relative to an incidence of 1.0 in the first year of life, the mean ratios across the five studies for the other four years were 0.58 (year 2), 0.48 (year 3), 0.31 (year 4) and 0.19 (year 5). These ratios were used to adjust reported incidences to the full 0–4 year age range when necessary.

Controlling for differences in study design

We needed to ensure that all of the longitudinal studies were measuring the same entity using comparable study designs or to introduce appropriate corrections if this was not the case. Our main concern was that differences in case definitions might

Box 1. Steps in the research plan

Step	Aim	No. of studies
1	Review all studies published from 1961 to 2001 that referred to acute respiratory infections, developing countries and children	2200
2	Select studies that either: <ul style="list-style-type: none"> • directly attempt to estimate incidence of clinical pneumonia in children younger than five years of age in developing countries, or • provide information that helps to understand the determinants of the occurrence of clinical pneumonia, its etiology, clinical features, management, case-fatality rates, and outcomes in developing countries 	308
3	Create electronic knowledge database that classifies information presented in the 308 studies into 30 different categories. This database is available from http://www.who.int/child-adolescent-health/New_Publications/Overview	308
4	Select studies that satisfy the criteria of: <ul style="list-style-type: none"> • community-based longitudinal studies • estimate the incidence of clinical pneumonia 	46
5	Further selection from these 46 studies of those that satisfy five pre-defined criteria: <ul style="list-style-type: none"> • community-based surveillance of a pre-defined population of children • study lasting a minimum of one year • active case detection • surveillance intervals of 2 weeks or shorter • case definitions clearly defined and consistently applied 	28
6	Identify studies from these 28 that: <ul style="list-style-type: none"> • were community-based longitudinal studies, and • reported the case-fatality rate for all episodes in a community 	4
7	Identify studies from these 28 that: <ul style="list-style-type: none"> • were community-based longitudinal studies and • reported the proportion of severe episodes of clinical pneumonia in all episodes of clinical pneumonia 	6
8	Identify studies from these 28 that: <ul style="list-style-type: none"> • were community-based or hospital-based studies, and • reported the case-fatality rate for severe episodes of clinical pneumonia 	12
9	Calculate the global estimate of the incidence of clinical pneumonia in children aged 0–4 years as: <ul style="list-style-type: none"> • median of incidence reported by 28 studies in Step 5 • overall mortality divided by the median case-fatality rate for all clinical pneumonia from studies in Step 6 • overall mortality divided by median case-fatality rate for severe clinical pneumonia from studies in Step 8 and by median proportion of severe episodes of clinical pneumonia in all episodes from studies in Step 7 	Not applicable

This yields three independent global estimates of incidence of acute lower respiratory infections in children aged 0–4 years.

produce estimates that were not comparable. A simple classification of ARI into three categories according to severity was proposed by WHO in 1985 to define a classification system that would be useful in community-based studies in developing countries (48). The WHO ARI classification system defines episodes of ARI as:

- (1) **severe** if there is cough and chest indrawing, cough and not being able to drink, or stridor at rest (requiring hospital referral);
- (2) **moderate** if there is cough and fast breathing but no chest indrawing (requiring home treatment with antimicrobials and supportive measures); or
- (3) **mild** if there is cough without fast breathing (≤ 50 breaths per minute) and no chest indrawing, with sore throat, ear discharge for more than 2 weeks and blocked or runny nose (requiring home treatment with supportive measures only).

In each of the 28 studies, we were primarily interested in determining whether clinical pneumonia was diagnosed by a non-physician (i.e., a trained field worker or lay reporter) or a physician or paediatrician. In these studies, trained field workers or lay reporters based their diagnosis of clinical pneumonia on whether a child had a respiratory rate at or above the threshold

of 50, or lower chest wall indrawing (which is included in the moderate or severe category of the WHO ARI classification), or both (49, 50). The physicians based their diagnosis on experience and supported it with chest auscultation to identify signs consistent with pneumonia or bronchiolitis.

Case definition

We aimed to investigate whether non-physicians were likely to overdiagnose cases regardless of how strict the criteria were that they used. Therefore, using their definition of a case, we divided all 28 studies into either category I (diagnosis established by non-physicians) or category II (diagnosis established by physicians). Our hypothesis was that studies in category II would generally report lower estimates of incidence. Table 1 (web version only, available at: <http://www.who.int/bulletin>) shows whether diagnosis was done by a physician or non-physician for the majority of cases of clinical pneumonia in the community by study.

To further explore the possible effects of differences in case definition on incidence, we studied the diagnostic criteria used within the group of studies in which non-physicians had the principal role in diagnosis (that is, category I studies). Among those we identified studies in which the diagnostic

criteria were based on WHO definition only (called category I-A) or also included 1–3 additional criteria, such as cyanosis or shock (called category I-B), or four or more such criteria (category I-C). We presumed that the more additional criteria there were, the lower the estimates should be. Also, in some studies within category I, case definitions also allowed for wheeze (classified as W+), which could bias the estimates upwards, or required crepitations to be heard on auscultation (designated as C+/R+), which might lower the estimates. Appendix 1 (web version only, available at: <http://www.who.int/bulletin>) gives further details on how we developed four case definition variables to explore the possible effects of these differences.

Understanding determinants of variation in incidence of clinical pneumonia

We treated all 28 studies as random data points from their specific setting within the developing world, each of which was needed to produce a global estimate. Thus, their results needed adjustment only for differences in study design and not for differences in settings. However, an additional attempt was made to improve our understanding of the determinants of variations in incidence by investigating the effects of 15 variables related to the design or setting of each study. Most of these variables were quantitative (altitude, annual rainfall, average annual temperature, median year of study, mean cohort size, duration of study and duration of surveillance intervals). These are shown in detail in Table 1 (web version only, available at: <http://www.who.int/bulletin>). Qualitative variables (information on population, who diagnosed clinical pneumonia, place of diagnosis, risk of malaria and ALRI case definition) were specifically categorized (Table 2 (web version only, available at: <http://www.who.int/bulletin>)).

To investigate the effect of case definition on the estimated incidence, four different case definition variables (CDV1–CDV4) were developed (Appendix 1, (web version only, available at: <http://www.who.int/bulletin>)). A number of other factors known to be related to the incidence of clinical pneumonia (such as prevalence of malnutrition, low birth weight, whether the child had been breastfed, incomplete vaccination status, or overcrowding at home) were not reported consistently enough to be included in the regression model (although their national prevalence was used in a subsequent study to produce estimates for WHO regions). The correlation between the 15 variables and the estimates of the incidence of clinical pneumonia was first investigated through univariate regression analysis. Because the number of studies included was relatively small, only the six variables that had the most significant correlation with incidence were entered into the multiple regression analysis. The other variables were omitted to ensure that the number of studies is approximately five times greater than the number of selected variables, to improve the statistical power of this analysis. Statistical analysis was done using Systat 7.0 for Windows software and the Poisson regression model.

Estimation of incidence and ranges

Because the incidence reported in the individual studies reflect only their specific settings, their results should not necessarily be viewed as representative of the country or region where the study took place. However, each study represents a valid incidence estimate from the surveillance of a number of populations in developing countries that are widely scattered across the world (Fig. 1). Our estimate of the incidence in develop-

ing countries is thus based on the median incidence from 28 community-based studies. The burden of clinical pneumonia among the minority of children less than five years old who live in developed countries (about 13% of children less than five years old worldwide (1)) was inferred from the population estimate for the year 2000 by the United Nations Population Division and population-based studies of the incidence of clinical pneumonia in the United States of America and the United Kingdom (3, 4).

We assessed the plausibility (and internal consistency with other related data) of the estimate for the developing world using two approaches. In the first approach, global ARI mortality was divided by the median, 25th and 75th percentile values of case-fatality rates for all clinical pneumonia reported in the literature. In the second approach, global ARI mortality was divided by the median, 25th and 75th percentile values of reported case-fatality rates only for severe cases of pneumonia, and also by the median, 25th and 75th percentile values of the proportions of all clinical pneumonia cases reported as severe (requiring admission to hospital).

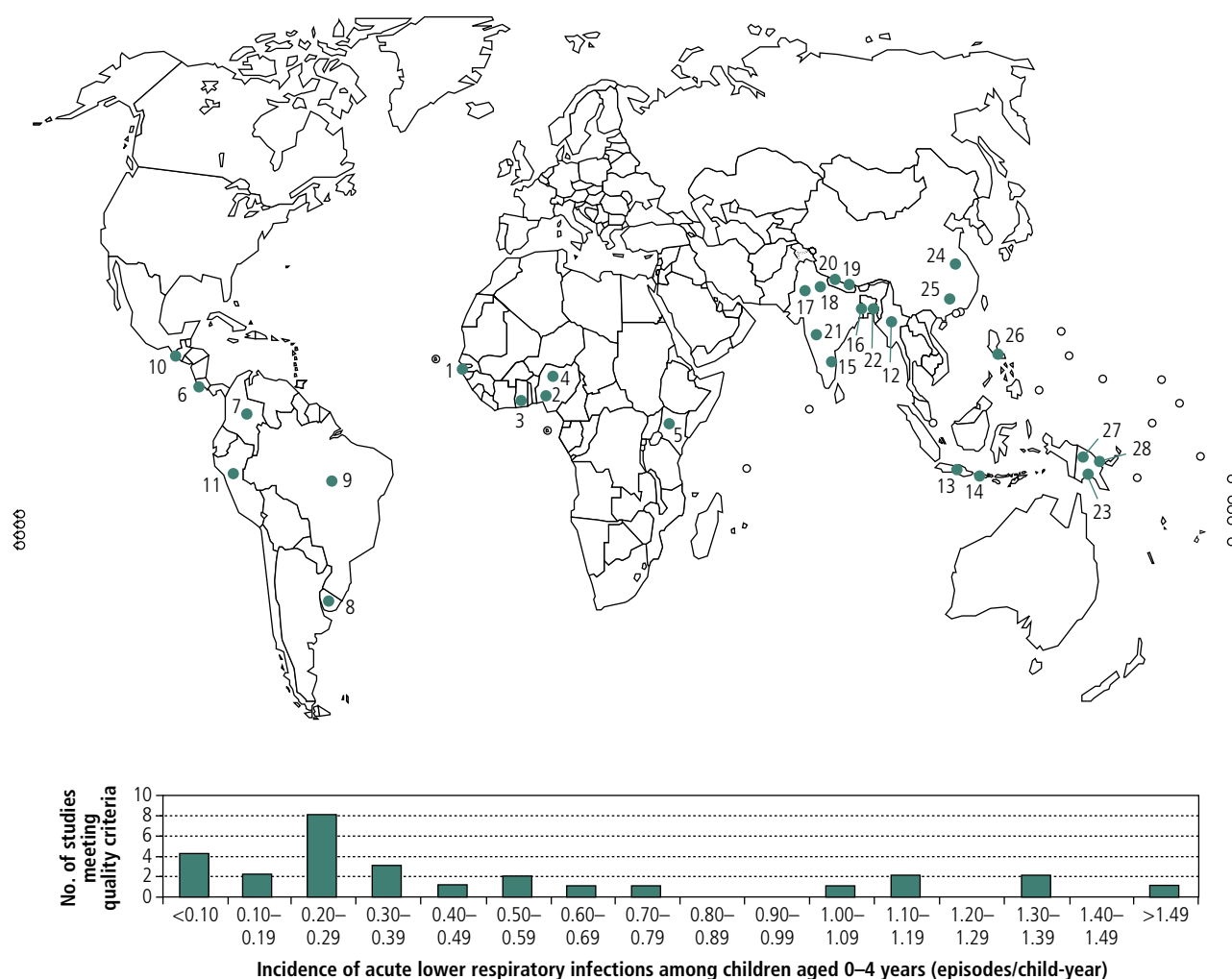
Results

Table 1 (web version only, available at: <http://www.who.int/bulletin>) summarizes the data on study design and incidence from the 28 studies that satisfied the inclusion criteria (5–32). They are listed in chronological order and classified according to WHO region. Most of the studies were performed in the following regions: the South-East Asia Region (11 studies; eight in subregion D and three in subregion B), the Western Pacific Region (six studies; all in subregion B), the African Region (four studies; all in subregion D), and the Region of the Americas (four studies; all in subregion B). Only two studies were available from subregion D of the Region of the Americas and only one study from subregion E of the African Region; none were available from the Eastern Mediterranean Region. (See <http://www.who.int/about/contactregional/en/> for details of WHO regions.)

The majority of studies (19; 68%) were performed in the late 1980s. Fourteen studies were performed in rural populations, seven in suburban areas, six in urban areas, and one study covered several different populations. Seven studies were carried out near sea level, while seven others investigated populations living at an altitude higher than 1500 m. The average annual rainfall at the study sites ranged from almost none in Peru to 2500 mm in Costa Rica. The mean annual temperatures ranged from 15 °C in China to 29 °C in Thailand. The period of follow-up was 1 year in 12 studies, 2 years in nine studies, and 3 years in seven studies. The size of the cohort was fewer than 300 children in six studies, 300–1000 in 12 studies, and more than 1000 in 10 studies. The surveillance intervals were weekly or more frequently in 18 studies (64%). In eight studies physicians or paediatricians established the diagnosis; in 11 diagnosis was performed solely by lay reporters or trained field workers; and in nine studies trained field workers were principally involved in establishing the diagnosis, but subsets of children under surveillance were checked or field workers were assisted by physicians. In 20 studies (71%) the incidence was reported across the full age range (0–4 years), while in eight it was adjusted as described earlier.

Two studies (from the Gambia and Peru) reported on both clinical pneumonia as defined by clinical criteria and radiologically confirmed pneumonia. These studies reported that

Fig. 1. Map showing the location of the 28 studies and the distribution of reported incidence of clinical pneumonia. (Numbers on the map refer to study numbers shown in Table 1 (web version only, available at: <http://www.who.int/bulletin>))



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the percentage of radiologically confirmed pneumonia was only 24–36% of the estimates of the incidence as measured by community surveillance.

Reports of the percentage of episodes considered severe from four studies ranged from 6–12%. The generalizability of these four studies is not known. (The mean incidence from these studies is higher than from all 28 studies.) The estimated incidence was less than 0.1 episode per child-year (e/cy) in four studies, 0.1–0.5 e/cy in 14 studies, 0.6–1.0 e/cy in four studies, and more than 1.0 e/cy in six studies. The variation in estimates of incidence seemed large and had a bimodal distribution (Fig. 1). However, this is perhaps not surprising given the wide variety of risk factors underlying the incidence of clinical pneumonia in developing countries. We considered these risk factors further in our subsequent study on incidence in different WHO regions. For the purpose of this study it was important to ensure that elements of study design (the case definition of clinical pneumonia in particular) were not responsible for systematic deviations in incidence. To account for this, a multiple regression analysis was performed to determine the effects of 15 study characteristics on incidence.

The multiple regression analysis of variables that could influence reported incidence was limited to those variables that were provided in the majority of published reports. The main purpose was to determine whether any further adjustment needed to be made to the incidence because the four case definitions significantly affected the estimates. In the initial univariate analysis, only the most basic difference in case definition (WHO criteria compared with physician's assessment) showed any correlation with reported incidence, but it was a rather weak correlation. In studies that allowed episodes of wheezing to be scored as clinical pneumonia or which extended the definition to also include findings on chest auscultation or additional rarer features of clinical pneumonia (such as cyanosis and heart failure), we were unable to demonstrate any significantly increased estimates of incidence under any model (Table 2, web version only, available at: <http://www.who.int/bulletin>).

In order to increase the statistical power of the analysis, given the small number of data points and the large number of variables, the six most significant predictors from the initial analysis were entered into the multiple regression analysis. This

showed that only annual rainfall and the place where the child was diagnosed were statistically significantly correlated with incidence. Since both of these factors reflect the setting of the study rather than the design of the study, we concluded that there was no need for further adjustment.

The effect of annual rainfall on overall incidence has not been reported previously. We investigated whether this effect might be due to the misclassification of malaria episodes (presenting as fast breathing) by categorizing studies by level of intensity of transmission of falciparum malaria. There was no evidence to support the idea of misclassification. Some of the alternative hypotheses to be explored further are the relationship of the amount of time children spend crowded together indoors, higher risks of transmission of respiratory infections in rainy climates and the greater bacterial superinfection of viral ARI episodes in humid conditions.

Table 3 presents the annual estimates of clinical pneumonia for the year 2000 for developing countries (where the total population of children aged 0–4 years is estimated to be 523.3 million) using the approaches described in the Methods section. The median estimate of incidence was 0.28 episodes per child-year. The 25–75% interquartile range of the estimate was 0.21–0.71 e/cy.

To check the plausibility of the main estimate we used two approaches. The first approach was based on global ARI mortality and reported case-fatality rates for all clinical pneumonia. This was less robust than the above estimate since we

could only identify four community-based studies that gave a valid estimate of the case-fatality rate. These estimates varied quite widely: 0.2%, 1.3%, 2.6% and 3.2% (21, 22, 33, 34). This yielded a median incidence of 0.20 e/cy (25–75% interquartile range 0.15–0.31).

The second approach was based on the proportion of cases of severe clinical pneumonia acquired in the community and the reported case-fatality rate for severe cases. Estimates of the case-fatality rate were available from 12 studies (26, 35–45) and ranged from 6.6–14.1%. Similarly, the proportion of severe community-acquired episodes was available from six community-based studies (5, 8, 20, 23, 46, 47) and ranged from 5.9–16.8%. This produced a median incidence of 0.44 e/cy with a range of 0.28–0.76 e/cy (based on the 25–75% interquartile ranges of case-fatality rates and of reported proportions of severe clinical pneumonia).

The ranges obtained by the main approach and the two ancillary approaches overlap between the values of 146 million and 159 million new episodes of clinical pneumonia per year. Giving the most weight to the estimate obtained through the main approach, but also taking into account the results of the other two approaches, the analyses suggest that the most plausible point of overlap is close to 0.29 e/cy. This equates to 150.7 million new cases of clinical pneumonia, 11–20 million (7–13%) of which are severe enough to require hospital admission.

We were unable to identify any population-based studies

Table 3. Global estimates of incidence (range) of clinical pneumonia in children aged 0–4 years. Incidence expressed as episodes/child-year (e/cy)

Approach	25th (or 75th) percentile ^a	Median	75th (or 25th) percentile ^b
Developing world (main approach)			
Incidence of clinical pneumonia measured directly (28 studies; refs 5–32)	0.205 e/cy	0.280 e/cy	0.710 e/cy
Annual no. of new cases of clinical pneumonia in millions (based on total population of children aged 0–4 years in developing world)	107.3	146.5	371.6
Plausibility check (approach 1)			
Case-fatality rate for all episodes of clinical pneumonia (4 studies; refs 21, 22, 33, 34)	2.60%	1.95%	1.30%
Related clinical pneumonia incidence (based on 2.1 million deaths annually; ref. 1)	0.152 e/cy	0.203 e/cy	0.305 e/cy
Annual No. of new cases of clinical pneumonia in millions (based on total population of children aged 0–4 years in developing world)	79.5	106.2	159.6
Plausibility check (approach 2)			
Case-fatality rate for episodes of severe clinical pneumonia (12 studies; refs 26, 35–45)	11.05%	9.90%	7.80%
Proportion of severe episodes of clinical pneumonia in all episodes (6 studies; refs 5, 8, 20, 23, 46, 47)	12.80%	9.20%	6.70%
Related clinical pneumonia incidence (based on 2.1 million deaths annually; ref. 1)	0.280 e/cy	0.435 e/cy	0.757 e/cy
Annual no. of new cases of clinical pneumonia in millions (based on total population of children aged 0–4 years in developing world)	146.5	227.6	396.2
Developed world			
Directly measure incidence of pneumonia (median of four estimates from large population-based studies in the USA and Europe; refs 3, 4, 52, 53)	NA ^c	0.026 e/cy	NA ^c
Annual no. of new cases of clinical pneumonia in millions (based on total population of children aged 0–4 years in developed world)	NA ^c	2.1	NA ^c

^a As a result of the inverse relationship between some variables in this table, this represents the 75th percentile if the results are presented in decreasing value over the percentile range.

^b As a result of the inverse relationship between some variables in this table, this represents the 25th percentile if the results are presented in decreasing value over the percentile range.

^c NA = not applicable.

from developed countries that used active surveillance and similar case definitions. In Table 3 we show the median estimate of incidence in young children reported in four large population-based studies in the United States and Europe. This median estimate of 0.026 e/cy (3, 4, 51, 52) is approximately 10% of the estimate of clinical pneumonia in developing countries, but these results are not directly comparable because the studies used different methods of case ascertainment and different definitions. However, this estimate represents 2.1 million cases of pneumonia occurring in a population of 81.6 million children less than five years old in developed countries (1).

The number of studies from developing countries that we judged to meet a limited number of essential quality criteria was small. Summarizing the findings of these studies is complicated by differences in their design and settings. Some of the communities being studied could have had particularly high mortality from ARI, thus further limiting the generalizability of the findings. None of the studies reported the incidence of clinical pneumonia in areas where there is a high prevalence of HIV. It is clear, therefore, that despite our efforts to identify valid estimates and to control for confounding and modifying factors, estimates of ALRI incidence in children in developing countries continue to be uncertain. In particular there is a need for studies to define current incidence in settings where HIV is a significant public health problem. The results of this review should therefore be interpreted with caution.

Conclusion

This review highlights the magnitude of the burden of clinical pneumonia in developing countries where often only mortality is considered. This study's definition of clinical pneumonia

encompassed the clinical conditions of pneumonia, bronchiolitis and reactive airways disease associated with respiratory infections (although the proportion of the episodes due to the latter was low in the populations discussed). These episodes result in acute suffering and short-term complications and have a detrimental effect on a child's nutritional status and may also influence the risk of other childhood diseases. In addition, a number of studies have suggested that clinical pneumonia in early childhood may have long-term consequences for respiratory function and health. This review demonstrates the substantial variation in annual incidence among young children in different settings. This points to the potential to intervene against risk factors to prevent clinical pneumonia and significantly reduce the large burden of disease in childhood resulting from clinical pneumonia. ■

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Conflicts of interest: none declared.

Résumé

Estimation de l'incidence mondiale de la pneumopathie clinique chez les enfants de moins de cinq ans

Objectif La pneumopathie clinique (définie comme l'ensemble des infections respiratoires associées à des signes cliniques de pneumopathie, principalement la pneumonie et la bronchiolite) chez l'enfant de moins de cinq ans reste la cause majeure de mortalité infantile dans le monde. Le but de cet article est d'estimer l'incidence mondiale de la pneumopathie clinique chez les jeunes enfants.

Méthodes L'estimation pour les pays en développement repose sur l'analyse des données publiées au sujet de l'incidence de la pneumopathie clinique et tirées d'études longitudinales en communauté. Les auteurs ont établi que, parmi les plus de 2000 études publiées depuis 1961, 46 rapportent l'incidence de la pneumopathie clinique et 28 répondent aux critères de qualité prédéfinis.

Résultats D'après ces études, l'incidence médiane est estimée à 0,28 épisode par enfant - année (ép./e.a.). L'intervalle interquartile 25-75 % correspond à 0,21-0,71 ép./e.a. Les auteurs ont évalué la plausibilité de cette estimation à partir d'estimations de la mortalité mondiale par infections respiratoires aiguës et des taux de létalité

indiqués pour l'ensemble des épisodes de pneumopathie clinique rapportés dans les études en communauté ou du taux de létalité indiqué uniquement pour les cas graves et des estimations de la proportion de cas graves survenant dans une population ou une communauté définie.

Conclusion D'après le recouvrement entre les intervalles de fiabilité des estimations, on peut conclure que 0,29 ép./e.a. constitue une estimation plausible de l'incidence de la pneumopathie clinique dans les pays en développement. Ce chiffre équivaut à une incidence annuelle de 150,7 millions de nouveaux cas, dont 11 à 20 millions (7 à 13 %) sont des cas suffisamment graves pour imposer une hospitalisation. On ne dispose pas de données comparables pour le monde développé. Cependant, des études en populations de grande ampleur indiquent que l'incidence des pneumopathies contractées dans la communauté chez les enfants de moins de cinq ans est d'approximativement 0,026 ép./e.a., ce qui laisse à penser que plus de 95 % de l'ensemble des épisodes de pneumopathie clinique chez les jeunes enfants dans le monde surviennent dans les pays en développement.

Resumen

Estimación mundial de la incidencia de neumonía clínica entre los menores de 5 años

Objetivo La neumonía clínica (definida como las infecciones respiratorias asociadas a signos clínicos de neumonía, principalmente neumonía y bronquiolitis) entre los menores de 5 años es todavía la principal causa de mortalidad en la niñez en el mundo. En este artículo hacemos una estimación de la incidencia mundial de neumonía clínica en los niños pequeños.

Métodos Nuestras estimaciones para los países en desarrollo se han basado en un análisis de los datos publicados en estudios longitudinales comunitarios sobre la incidencia de neumonía clínica. Entre los más de 2000 estudios publicados desde 1961, identificamos 46 en los que se notificaba la incidencia de neumonía clínica, 28 de los cuales reunían los criterios de calidad preestablecidos.

Resultados La incidencia mediana estimada obtenida a partir de esos estudios fue de 0,28 episodios por niño y año (e/na). El intervalo intercuartílico 25%-75% fue de 0,21–0,71. Evaluamos la verosimilitud de esos valores empleando estimaciones de la mortalidad mundial por infecciones respiratorias agudas y las tasas de letalidad registradas para todos los episodios de neumonía

clínica notificados en estudios comunitarios, o bien la tasa de letalidad notificada sólo para los casos graves y las estimaciones de la proporción de casos graves que ocurrían en una determinada población o comunidad.

Conclusión Considerando el solapamiento de los márgenes de las estimaciones, una estimación verosímil de la incidencia de neumonía clínica en los países en desarrollo es la cifra de 0,29 e/na. Esto equivale a una incidencia anual de 150,7 millones de casos nuevos, de los cuales unos 11-20 millones (7%–13%) son suficientemente graves para requerir hospitalización. En el mundo desarrollado no se dispone de datos comparables. Sin embargo, diversos estudios poblacionales muestran que la incidencia de neumonía adquirida en la comunidad entre los niños menores de cinco años es aproximadamente de 0,026 e/na, lo que lleva a pensar que más del 95% de todos los episodios de neumonía clínica que sufren los niños pequeños en todo el mundo se dan en los países en desarrollo.

ملخص

تقدير معدل الوقوع العالمي للالتهاب الرئوي السريري (الإكلينيكي) لدى الأطفال دون سن الخامسة

الالتهابات التنفسية الحادة، وإلى معدلات وفيات الحالات المبلغ عنها والناجمة عن جميع حالات الالتهاب الرئوي السريري (الإكلينيكي) المبلغ عنها في الدراسات المرتكزة على المجتمع أو معدلات وفيات الحالات المبلغ عنها في الحالات الوحيدة فقط، وإلى تقديرات النسب المئوية للحالات الوحيدة التي تحدث في مجموعة سكانية محددة أو مجتمع محدد.

الخلاصة: إن وجود التراكم بين مجالات التقديرات يشير إلى أن التقدير المقبول لمعدل وقوع الالتهاب الرئوي السريري (الإكلينيكي) في البلدان النامية يعادل ٠,٢٩ إصابة لكل طفل في السنة، وهذا يعادل وقوع ١٥٠,٧ مليون حالة حديثة في السنة، منها ١١ – ٢٠ مليون حالة (أي بنسبة ٧ – ١٣%) على درجة من الوخامة تتطلب الإدخال إلى المستشفيات. ولا تتوافر في العالم المتقدم معطيات يمكن المقارنة معها، إلا أن الدراسات المجراة على مجموعات سكانية كبيرة تشير إلى أن معدل وقوع الالتهاب الرئوي المكتسب في المجتمع بين الأطفال دون عمر خمس سنوات تقارب ٠,٠٢٦ إصابة لكل طفل في السنة، وهذا يشير إلى أن أكثر من ٩٥% من مجموع الإصابات بالالتهاب الرئوي السريري (الإكلينيكي) لدى صغار الأطفال في العالم يحدث في البلدان النامية.

المهدف: يعرف الالتهاب الرئوي السريري (الإكلينيكي) بأنه التهاب في الجهاز التنفسي يترافق مع علامات التهاب الرئة، وبشكل أساسي الالتهاب الرئوي والتهاب القصيبات، لدى الأطفال دون سن الخامسة، وهو لا يزال السبب الرئيسي لوفايات الأطفال في العالم. ومهدف في هذه الورقة إلى تقدير معدل الوقوع العالمي للالتهاب الرئوي السريري (الإكلينيكي) لدى صغار الأطفال.

الطريقة: تركزت تقديراتنا في البلدان النامية على تحليل للمعطيات المنشورة حول معدل وقوع الالتهاب الرئوي، الناتجة من دراسات طولية مرتكزة على المجتمع. ومن بين ما يزيد على ألفي دراسة منشورة منذ عام ١٩٦١ تعرفنا على ٤٦ دراسة أبلغت عن وقوع الالتهاب الرئوي السريري (الإكلينيكي)، وقد حققت ٢٨ دراسة من هذه الدراسات معايير الجودة المحددة مسبقاً.

الموجودات: يقدر أن معدل الوقوع الوسطي المستنتج من هذه الدراسات يبلغ ٠,٢٣ إصابة لكل طفل في السنة. وتراوح المدى الرئوي للنسبة ٢٥% إلى ٧٥% من ٠,٢١ إلى ٠,٧١. وقد قمنا بتقييم مدى مقبولة هذه التقديرات بالرجوع إلى تقديرات معدلات الوفيات العالمية الناجمة عن

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Table 1. Summary of 28 studies that satisfied inclusion criteria and were used to estimate the incidence of clinical pneumonia

Study no. ^a	Authors and reference no.	Year published	Country	Setting	Malaria risk	Population type	Altitude/rainfall/temp.	Study period	Cohort	Surveillance intervals	Person making diagnosis ^b	Case definition category ^c	Site of diagnosis	Incidence of acute lower respiratory infections ^d
African Region, subregion D														
1	Campbell et al. (5)	1989	Gambia	Basse	High	Rural	10m/975mm/27 °C	12 months (03/87–03/88)	491 children aged 0–4 years	Weekly	TFW (and physician)	I B, W–, C/R–	Home and hospital	Age 0–4 years: 0.45/cy; Age 0–4 ^{xr} years: 0.16/cy
2	Oyejide & Osinusi (6)	1990	Nigeria	Ibadan	High	Urban	200m/1637mm/28 °C	36 months (10/84–10/87)	400 children aged 0–4 years	Weekly	FW (and physician)	I C, W–, C/R+	Clinic and home	Age 0–4 years: 0.22/cy; Age 0–4 ^{ml} years: 0.08/cy
3	Afari et al. (7)	1991	Ghana	Central Ghana	High	Rural	300m/1100mm/27 °C	36 months (01/87–12/89)	440 children aged 0–4 years	Weekly	Nurses (and physician)	I B, W–, C/R–	Clinic and home	Age 0–4 years: 0.06/cy
4	Fagbule et al. (8)	1994	Nigeria	Ilorin, Kwara state	High	Suburban	150m/1100mm/28 °C	12 months (07/88–06/89)	481 children aged 0–4 years	3x / week	TFW	I A, W+, C/R–	Home	Age 0–4 years: 1.30/cy
African Region, subregion E														
5	Wafula et al. (9)	1990	Kenya	Maragua	None	Rural	1650m/1200mm/18 °C	36 months (02/85–01/88)	470 children aged 0–4 years	Weekly	FW (and physician)	I C, W–, C/R+	Clinic and home	Age 0–4 years: 0.21/cy
Region of the Americas, subregion B														
6	James (10)	1972	Costa Rica	San Jose	Low	Suburban	1170m/2500mm/21 °C	12 months (03/66–04/67)	137 children aged 0–4 years	Weekly	Physician	II	Home	Age 0–4 years: 0.04/cy; Age 0–4 ^{mn} years: 0.46/cy
7	Borrero et al. (11)	1990	Colombia	Cali	Low	Urban	1100m/1000mm/25 °C	36 months (01/87–12/89)	340 children aged 0–1.5 years	Weekly	TFW	I C, W–, C/R+	Clinic	Age 0–1.5 years: 1.71/cy; Age 0–4 ^{la} years: 1.02/cy
8	Hortal et al. (12)	1990	Uruguay	Montevideo	None	Urban	22m/1075mm/16 °C	32 months (05/85–12/87)	166 children aged 0–2 years	10 days	Paediatrician	II	Home	Age 0–2 years: 1.80/cy; Age 0–4 ^{la} years: 1.17/cy
9	Barreto et al. (13)	1994	Brazil	Serrinha, Bahia state	None	Urban	90m/1346mm/23 °C	12 months (12/90–12/91)	1 240 children aged 0.5–3 years	Fort-nightly	Paediatrician (with FW)	II	Home and hospital	Age 0.5–3 ^{la} years: 0.26/cy; Age 0–4 ^{la} years: 0.21/cy
Region of the Americas, subregion D														
10	Cruz et al. (14)	1990	Guatemala	Guatemala City	None	Suburban	1480m/1346mm/21 °C	24 months (01/85–12/86)	521 children aged 0–4 years	Fort-nightly	TFW (and physician)	I C, W–, C/R+	Clinic	Age 0–4 years: 0.31/cy
11	Lanata et al. (15)	1994	Peru	Canto Grande, Lima	None	Suburban	154m/0 mm/22 °C	27 months (07/87–10/89)	1500 children aged 0–2.5 years	2x / week	Physician (and TFW)	II	Home and clinic	Age 0–3 ^{xr} years: 0.08/cy; Age 0–4 ^{la} years: 0.25/cy
South-East Asia Region, subregion B														
12	Vathanophas et al. (16)	1990	Thailand	Bangkok	Low	Urban	2m/400mm/29 °C	24 months (01/86–12/87)	674 children aged 0–4 years	2x / week	TFW (and physician)	I C, W–, C/R+	Home	Age 0–4 years: 0.07/cy

(Table 1, cont.)

Study no. ^a	Authors and reference no.	Year published	Country	Setting	Malaria risk	Population type	Altitude/rainfall/temp.	Study period	Cohort	Surveillance intervals	Person making diagnosis ^b	Case definition category ^c	Site of diagnosis	Incidence of acute lower respiratory infections ^d
13	Kartasasmita et al. (17)	1995	Indonesia	Cikutra, Bandung	Low	Suburban	770m/2000mm/27 °C	12 months (06/89–05/90)	269 children aged 1–3.5 years	Fort-nightly	PHCW paediatrician	I C, W–, C/R+	Home	Age 1–3.5 years: 2.00/cy; Age 0–4 ^{IA} years: 2.45/cy
14	Dibley et al. (18)	1996	Indonesia	Southern Central Java	None	Rural	1500m/1000mm/24 °C	20 months (09/89–05/91)	1407 children aged 0.5–4 years	3x / week	TFW	I A, W+, C/R–	Home	Age 0.5–4 years: 0.10/cy; Age 0–4 ^{IA} years: 0.11/cy
South-East Asia Region, subregion D														
15	Kamath et al. (19)	1969	India	Vellore	Low	Suburban	204m/1053mm/28 °C	21 months (06/65–09/67)	122 children aged 0–4 years	2x / week	Physician (and nurse)	II	Home	Age 0–4 years: 0.22/cy
16	Black et al. (20)	1982	Bangladesh	Matlab	High	Rural	0m/1500 mm/25 °C	12 months (03/78–03/79)	197 children aged 0–4 years	3x / week	Physician (and FW)	II	Home	Age 0–4 years: 1.10/cy
17	Datta et al. (21)	1987	India	Haryana, Ambala	Low	Rural	274m/1100mm/23 °C	21 months (01/82–09/83)	347 children aged 0–1 years	Weekly	TFW	I B, W+, C/R–	Home	Age 0–1 ^{MN} years: 0.35/cy; Age 0–4 ^{IA} years: 0.18/cy
18	Reddaiah & Kapoor (22)	1988	India	Haryana	Low	Rural	274m/1100mm/23 °C	12 months (01/86–12/86)	5 078 children aged 0–4 years	Fort-nightly	TFW	I B, W–, C/R+	Home	Age 0–4 years: 0.54/cy
19	Pandey et al. (23)	1989	Nepal	Kathmandu	None	Rural	2000m/1300mm/20 °C	36 months (02/84–01/87)	1 019 children aged 0–4 years	Fort-nightly	TFW	I B, W+, C/R+	Home	Age 0–4 years: 0.25/cy
20	Pandey et al. (24)	1991	Nepal	Yumla	None	Rural	2500m/1300mm/20 °C	36 months (06/86–06/89)	13 404 children aged 0–4 years	Fort-nightly	TFW	I A, W+, C/R–	Home	Age 0–4 years: 0.75/cy
21	Singh and Nayar (25)	1996	India	Wardha district, Maharashtra	Low	Rural	234m/600mm/27 °C	12 months (09/90–08/91)	384 children aged 0–4 years	Fort-nightly	Not reported (probably TFW)	I A, W+, C/R–	Home	Age 0–4 years: 0.07/cy
22	Zaman (26)	1997	Bangladesh	Matlab	High	Rural	0m/1500mm/25 °C	12 months (05/88–04/89)	696 children aged 0–4 years	2 times/ week	TFW	I B, W–, C/R–	Home	Age 0–4 years: 0.23/cy
Western Pacific Region, subregion B														
23	Riley et al. (27)	1983	Papua New Guinea	Tari and Asaro	None	Rural	1700m/4000mm/18 °C	12 & 48 months (72–73, 79–83)	1 595 and 1 000 children aged 0–4 years	Fort-nightly	TFW (and physician)	I B, W–, C/R–	Home and hospital	Age 0–4 years: 0.67/cy
24	Zhang et al. (28)	1986	China	Changping County	None	Semirural	17m/630mm/15 °C	24 months (06/81–06/83)	526 children aged 0–11 years	Weekly	Physician	II	Home, primary school	Age 0–4 years: 0.33/cy
25	Zeng et al. (29)	1988	China	Not applicable (various)	Various	Various	Various	12 months (01/85–12/85)	1 312 children aged 0.5–6 years	Daily	Physician	II	Nursery	Age 0.5–6 years: 0.30/cy; Age 0–4 ^{IA} years: 0.37/cy
26	Tupasi et al. (30)	1990	Philippines	Albang, Manila	Low	Urban	14m/2082mm/27 °C	24 months (04/85–03/87)	1 978 children aged 0–4 years	Weekly	Nurse (and physician)	I C, W–, C/R+	Home and clinic	Age 0–4 years: 0.57/cy

(Table 1, cont.)

Study no. ^a	Authors and reference no.	Year published	Country	Setting	Malaria risk	Population type	Altitude/rainfall/temp.	Study period	Cohort	Surveillance intervals	Person making diagnosis ^b	Case definition category ^c	Site of diagnosis	Incidence of acute lower respiratory infections ^d
27	Lehmann et al. (31)	1991	Papua New Guinea	Tari Basin	None	Rural	1700m/2000mm/18 °C	25 months (10/81–11/83)	2 000 children aged 0–9 years	Fort-nightly	Lay reporters	I B, W+, C/R–	Home and hospital	Age 0–4 years: 0.20/cy; Age 0–4 ^{PV} years: 0.15/cy
28	Lehmann et al. (32)	1992	Papua New Guinea	Asaro Valley	None	Rural	1700m/2000mm/18 °C	36 months (01/85–12/87)	156 children aged 0–4 years	2 times/week	Lay reporters	I B, W+, C/R–	Home	Age 0–4 years: 1.30/cy

^a To find out more about WHO regions and subregions see <http://www.who.int>.

^b For the person diagnosing clinical pneumonia, the following abbreviations are used: TFW = Trained field worker; FW = Field worker with no training; PHCW = primary health care worker.

^c For the case definition category, the following abbreviations are used: I A–C = WHO definitions; II = Physician's assessment; W+ = Wheeze part of case definition; W– = Wheeze not part of case definition; C+/R+ = Crepitations/rales part of definition of acute lower respiratory infection; C–/R– = Crepitations/rales not part of definition of acute lower respiratory infection; XR = X-ray confirmed; MI = Measles immunized; MN = Malnourished; IA = Incidence adjusted to full 0–4 year age range; VA = Vitamin A supplementation administered; PV = Pneumococcal vaccine administered.

^d Incidence expressed as episodes/child-year (e/cy).

Table 2. Correlation coefficients between 15 variables from 28 selected studies and incidence of clinical pneumonia

Variable no.	Description of variable	Correlation coefficient	Correlation coefficient > 0.50 between variables	Standardized multiple regression coefficient (β)	P-value
1	Calendar year of study (median if longer than 1 year)	0.165	-0.52 (variable 11)	0.529	0.069
2	Population type (categorized as rural, suburban or urban)	0.116	-0.54 (variable 12); -0.51 (variable 14)	0.201	0.309
3	Altitude (m)	0.048	-0.51 (variable 5); -0.55 (variable 6)	NA	NA
4	Annual rainfall (mm)	0.240	NA ^a	0.607	0.026
5	Average annual temperature (°C)	0.010	-0.51 (variable 3); 0.79 (variable 6)	NA	NA
6	Risk of malaria (categorized as none, low or high)	0.048	-0.55 (variable 3); 0.79 (variable 5)	NA	NA
7	Duration of follow-up (months)	-0.087	NA	-0.040	0.844
8	Cohort size	0.019	NA	NA	NA
9	Surveillance intervals (days)	0.066	NA	NA	NA
10	Person making diagnosis	-0.083	0.54 (variable 12); 0.64 (variable 13)	NA	NA
11	Case definition variable 1 (non-physician applying WHO definition vs physician using auscultation)	-0.168	-0.52 (variable 1); 0.76 (variable 12); 0.80 (variable 13); 0.82 (variable 14)	0.164	0.548
12	Case definition variable 2 (same as variable 11 above, but corrected for additional diagnostic criteria used)	-0.026	0.54 (variable 2); 0.54 (variable 10); 0.76 (variable 11); 0.90 (variable 13); 0.92 (variable 14)	NA	NA
13	Case definition variable 3 (same as variable 11 above, but corrected for inclusion of wheeze in definition)	-0.091	0.64 (variable 10); 0.80 (variable 11); 0.90 (variable 12); 0.85 (variable 14)	NA	NA
14	Case definition variable 4 (same as variable 11 above, but corrected for inclusion of crepitations/rales in definition)	-0.046	0.51 (variable 2); 0.82 (variable 11); 0.92 (variable 12); 0.85 (variable 13)	NA	NA
15	Place of diagnosis (categorized as home, clinic or hospital)	-0.226	NA	-0.465	0.035
Summary of multiple regression analysis^a		R = 0.581; R ² = 0.338;	Adjusted R ² = 0.139; SE = 0.513;	F ratio = 1.698;	P = 0.173

^a NA = not applicable.^b R = multiple regression for the model; R² = non-adjusted proportion of variance explained; Adjusted R² = adjusted proportion of variance explained; SE = standard error of the estimate; F ratio = analysis of variance.

Appendix 1. Case definition variables^a

Assigned value	Case definition variable 1 ^b	Case definition variable 2	Case definition variable 3	Case definition variable 4
1	The majority (or all) cases of clinical pneumonia in a community were diagnosed by a non-physician using WHO definitions ^c	Definition as for CDV1 with an assigned value of 1 plus WHO definition applied without any additional diagnostic criteria	Definition as for CDV1 with an assigned value of 1 but WHO definition (with or without additional diagnostic criteria) included wheeze	Definition as for CDV1 with assigned value of 1 but WHO definition (with or without additional diagnostic criteria) did not include crepitations or rales
2	The majority of cases of clinical pneumonia in a community were diagnosed by physicians or paediatricians using their own clinical assessment (relying on auscultation) ^d	Definition as for CDV1 with assigned value of 1 plus WHO definition applied with 1–3 additional diagnostic criteria (such as cyanosis, shock, heart failure)	Definition as for CDV1 with assigned value of 1 but WHO definition (with or without additional diagnostic criteria) did not include wheeze	Definition as for CDV1 with assigned value of 1 but WHO definition (with or without additional diagnostic criteria) also included crepitations or rales
3	NA ^e	Definition as for CDV1 with assigned value of 1 and WHO definition applied with four or more additional diagnostic criteria (such as cyanosis, shock, heart failure)	The majority of cases of clinical pneumonia in a community were diagnosed by physicians or paediatricians based on their own clinical assessment (relying on auscultation)	The majority of cases of clinical pneumonia in a community were diagnosed by physicians or paediatricians based on their own clinical assessment (relying on auscultation)
4	NA	The majority of cases of clinical pneumonia in a community were diagnosed by physicians or paediatricians based on their own clinical assessment (relying on auscultation)	NA	NA

^a For all case definitions the variables move from looser definitions to stricter definitions so that a negative correlation with the estimates of incidence is expected.

^b CDV1 = Case definition variable 1; CDV2 = Case definition variable 2; CDV3 = Case definition variable 3; CDV4 = Case definition variable 4.

^c Due to the variability in approaches found for this assigned value, case definition variables 2–4 are further defined and categorized in an attempt to achieve a greater correlation coefficient with the resulting incidence.

^d There was less variability in approaches for this assigned value. It was expected to give lower estimates than any further subcategory of case definition variable 1, assigned value 1. Therefore, for case definition variables 2–4, this assigned value (case definition variable 1, assigned value 2) remains unchanged.

^e NA = not applicable.

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